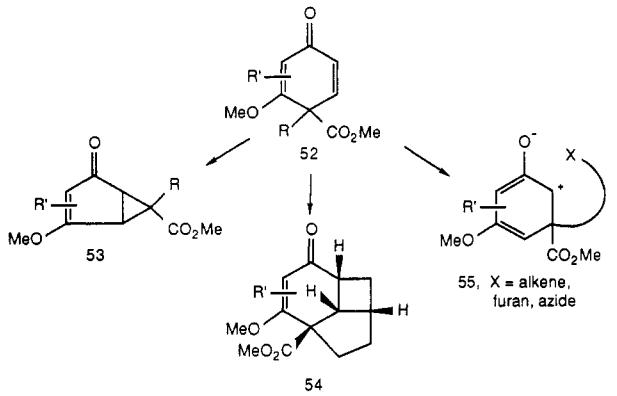
4-(3′-alkenyl) or 4-(3′-pentynyl) groups undergo efficient 2 + 2 photocycloaddition to give fused cyclobutanes of type **54**.[39] We have been particularly interested in the development of new intramolecular cycloaddition chemistry of oxyallyl zwitterions **55** that are generated by photorearrangement of bicyclohexenones **53**.[40,41]



Thus, a remarkable array of carbocyclic and heterocyclic ring systems are available by simple and generally efficient reactions of 2,4- and 2,5-cyclohexadien-1-ones. The stereoselective reductive alkylations of substrates such as 1 and 4 have played an important role in the elucidation of synthetic and mechanistic aspects of the indicated photorearrangements and cycloadditions.[12,36-39]

Concluding Remarks

The basic stereochemical consequences of the method have been established, models to explain stereocontrol have been formulated, and synthetic applications that begin to define the potential of the strategy have been completed. Despite these advances, it seems that we have only scratched the surface. Other modes of enolate reactivity should be examined; enolate oxidations, aminations, and condensation reactions will offer unique synthetic opportunities. A better understanding of enolate reactivity and aggregation effects is expected to evolve from the next generation of chemical and spectroscopic studies.

Synthetic applications to date have been confined to issues of stereocontrol in targeted cyclohexane rings, but incorporation of ring contraction and expansion techniques will extend the scope of the methodology. Inasmuch as cyclohexenes and cyclohexanones undergo a multitude of ring-cleavage reactions, it is expected that enantiomerically pure polyhydroxylated acyclic materials and novel α-amino acids and α-hydroxy acids will be available by relatively straightforward modifications of the chemistry described in this Account.

It is a pleasure to acknowledge the very significant contributions of graduate and postdoctoral students; their names are recorded in the references. Support from the National Institutes of Health (Grants GM 26568 and GM 33061) is appreciated.

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Quadrupole Ion Trap Mass Spectrometry

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In 1956 Paul described a device for containing gaseous ions in a small volume using only electric fields.[1] Three electrodes, two end-cap electrodes and a central ring electrode, each of hyperbolic cross section, form a chamber within which ions can be confined (Figure 1). Application of a radio-frequency (rf) voltage to the ring electrode establishes a quadrupole electric field in which the force on an ion is proportional to its distance from the center of the device; this allows ions of appropriate mass-to-charge ratios to have stable trajectories within the chamber and to be trapped for many seconds. This apparatus, the "Paul trap" or the "quadrupole ion trap", quickly came to be used for mass spectrometry[2] and for spectroscopy of stored ions.[3] For their pioneering work with ion traps, Wolfgang Paul of the University of Bonn and Hans Dehmelt of the University of Washington shared in the 1989 Nobel Prize for physics. As a mass spectrometer, the ion trap was and still is overshadowed by the quadrupole mass filter, also first described by Paul.[4]

In 1984 the first commercial quadrupole ion trap, based on a new method[5] of selectively ejecting ions of

A cooperative effort was undertaken in 1984 between Purdue University and Finnigan Corporation to construct an ion-trap mass spectrometer capable of performing MS/MS experiments. It is not difficult to persuade students from the middle west to spend time in California, and graduate student John Louris spent a number of months at San José in 1985 assisting John Syka and George Stafford in building this instrument, which became the prototype of the commercial ion-trap mass spectrometer (ITMS). This Account picks up the story at this point, illustrating fundamental studies of ion chemistry and applications to chemical analysis of this newest breed of mass spectrometers.

Ray Kaiser has just completed his Ph.D. degree in Analytical Chemistry and has accepted a position with Eli Lilly, Indianapolis, IN. Graham Cooks is Henry B. Hass Distinguished Professor of Chemistry.

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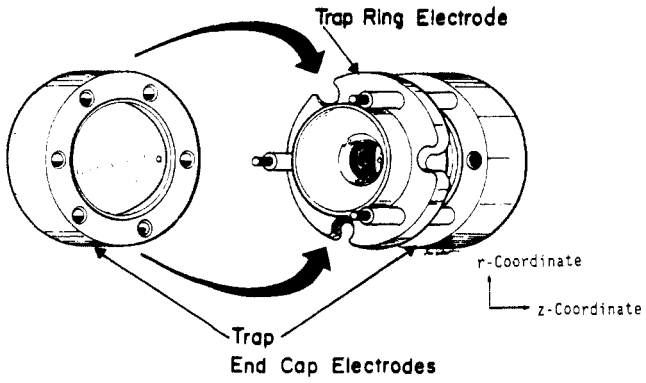

Figure 1. The ion-trap assembly showing the trapping cavity formed between the ring and end-cap electrodes. Reprinted with permission from ref 9. Copyright 1987 American Chemical Society.

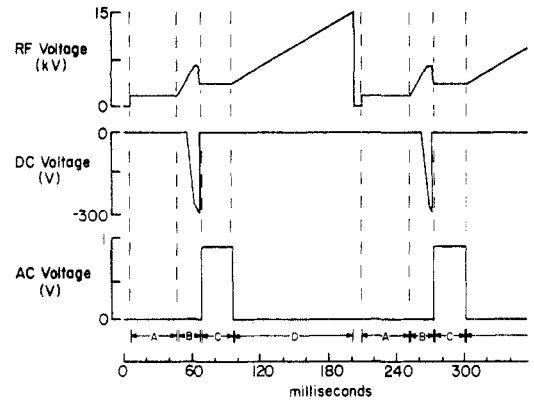

Figure 2. Time scale of ion-trap operation to record daughter (MS/MS) spectra. Ionization occurs during period A, parent ion isolation occurs in period B, daughter ions are generated in period C, and the mass analysis scan is performed in period D.

increasing mass-to-charge ratios (m/z) from the trap, was introduced as an inexpensive and sensitive mass spectrometric detector for gas chromatography. By application of an rf voltage of appropriate magnitude and frequency to the ring electrode, ions covering a broad range of masses are trapped. For the recording of a mass spectrum, the amplitude of the rf voltage is increased; this causes ions of increasing m/z to become unstable as their excursions within the potential well created in the chamber increase in amplitude and eventually take them beyond the physical bounds of the device. At this point they are ejected in mass sequence from the device through perforations in an end-cap.

At present, the Paul ion trap is undergoing such rapid development that it is possible that it might become *the* principal type of mass spectrometer in the future. This article provides an account of these developments, which include capabilities for mass-selecting and resonantly exciting ions of a particular m/z ratio, compatibility with laser-based experiments such as photodissociation, a mass/charge range in excess of 45 000, and such exquisite sensitivity that a sample of just 10^8 molecules of a peptide can yield both a mass spectrum and MS/MS data, including structurally diagnostic sequence ions. Emphasis is on work from this laboratory, but our debt to the few groups[6] active during the interregnum between the Paul studies a quarter century ago and the introduction of the commercial ion trap in 1984 is gratefully acknowledged.

The new capabilities of ion traps cover topics of great interest in mass spectrometry as a whole, namely, extension of the mass range, increased sensitivity, access to ion/molecule reactions as well as collision-activated dissociation, and availability of a wide range of ionization methods. Tandem mass spectrometry, in particular, has been a major growth point in mass spectrometry for more than a decade because it allows analysis of complex mixtures as well as studies of gaseous ion structure and reactivity.[7] The experiment has been implemented by using a variety of mass spectrometers, including sector mass analyzers, quadrupoles, time-of-flight devices, and combinations of each. Temporal separation of ions forms the basis of a tandem mass spectrometry experiment in a different type of ion trap, the ion cyclotron resonance (ICR) instrument. In this magnetic trap, ions are mass-selected and reacted and their products mass-analyzed later in time but in the same device.[8] The development of an MS/MS capability in the simple Paul electric ion trap was a major motivation of the present work.

Multiple Stages of Mass Spectrometry

Mass analysis in the ion trap is governed by the equation

$$m/z = 4V/(q_{\text{eject}} r_0^2 \Omega^2) \qquad (1)$$

where m/z is mass-to-charge ratio, V is the amplitude of the rf voltage applied to the ring electrode (7500 $V_{0\text{-}p}$ in these experiments), q_{eject} is the point on the Mathieu stability diagram[4] where ions become unstable under the influence of the rf-only field and are ejected into the detector ($q_{\text{eject}} = 0.91$), r_0 is the internal radius of the ion trap (here 1 cm), and Ω is the angular component of the rf drive frequency (1.1 MHz). Ions of larger mass-to-charge ratios remain stored in stable trajectories.[5,6] The physical and operating parameters of the instrument dictate the highest mass/charge range that may be analyzed.

In order to perform an MS/MS experiment, it is first necessary to isolate the parent ion whose daughter spectrum is to be recorded. This is done by operating the ion trap in the mode in which their two-dimensional analogues, quadrupole mass filters, are normally operated. A combination of rf and dc voltages is applied to the ring electrode, establishing a condition in which only ions in a narrow mass range are stable. This selected population of ions has a characteristic secular frequency of motion related to the stability parameter q. In an experiment analogous to a two-dimensional NMR experiment, the stored ions are irradiated by using a supplementary ac voltage having a frequency chosen to match their secular frequency of motion.[9] Absorption of energy increases the kinetic energy of the ions, and because ion traps are operated in a helium bath gas, this kinetic energy is converted into internal energy through collisions with helium. These collisions may cause dissociation of the selected parent ion by the process of collision-activated dissociation (CAD), and

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the population of fragment ions is then scanned to record the daughter MS/MS spectrum of the selected ion. Note that the parent ion is *selectively* excited since only it has an appropriate secular frequency to absorb energy from the supplementary ac signal. Figure 2 summarizes this experiment, showing how the combination of rf, dc, and supplementary ac voltages is applied to the electrodes in a sequence appropriate for recording a daughter spectrum.

The efficiency with which parent ions can be converted to daughters is a crucial criterion in MS/MS. Not only are ion traps inherently very sensitive mass spectrometers but in many cases dissociation efficiencies approach 100%, a level of performance that contrasts strongly with that achieved in other types of tandem mass spectrometers. For example, the tetraethylsilane radical cation fragments by the reaction sequence 2. At an ac excitation voltage of 1.0 V, ap-

$$[Si(C_2H_5)_4]^{\bullet+} \xrightarrow{\epsilon_0 = 0.5\ eV} [Si(C_2H_5)_3]^+ \xrightarrow{\epsilon_0 = 2.0\ eV} [HSi(C_2H_5)_2]^+ \xrightarrow{\epsilon_0 = 2.5\ eV} [H_2Si(C_2H_5)]^+ \quad (2)$$

plied for 5 ms, the molecular ion is *quantitatively* converted to $Si(Et)_3^+$ (85%), $HSi(Et)_2^+$ (10%) and H_2SiEt^+ (5%). Since the amount of energy required to yield particular fragment ions is known, the degree of fragmentation can be used to calibrate the amount of internal energy deposited.[10] When an ac excitation voltage of 3 V is used, internal energy in excess of 3.5 eV is deposited into the parent ion, as seen from the fragmentation of m/z 144 to yield m/z 59, a process that requires 3.5 eV. Note that the desired degree of excitation delivered to the ion can be dialed in, simply by varying the amplitude of the excitation voltage (or the time for which excitation is performed). The amount of energy required to cause dissociation of large biomolecules in a sector MS/MS instrument has been estimated to be very large (tens of electronvolts)[11] but the requirement for high internal energies is largely a consequence of the short time in which fragmentation must occur in order for the products to be observed. The relatively long time scale of the ion trap means that much smaller internal energies are required to fragment biomolecules as shown below.

The very high efficiency of CAD in the ion trap allows multiple stages of CAD to be performed *in sequence* by adding additional rf–dc selection steps prior to mass analysis.[12] For example, a particular daughter ion from an MS/MS spectrum can be isolated and activated to yield granddaughter ions in an MS^3 experiment. This sequence of parent ion isolation steps followed by dissociation steps can be repeated many times. Figure 3 illustrates an MS^6 spectrum—five stages of parent isolation and activation—of tetraethylsilane, showing the sequential losses of ethyl or ethylene groups from the selected and activated ions. The last activation step results in formation of SiH^+ (m/z 29) by loss of H_2 from SiH_3^+ (m/z 31). The experiment is valuable in studies of ion chemistry, for example, in confirming the reaction of protonated 2,2,6-trimethylcyclohexanone to form protonated acetone (m/z 59) through extensive skeletal rearrangement.[13] In another study, the cholesterol

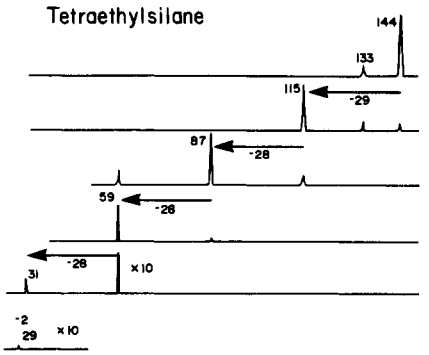

Figure 3. Consecutive activation (MS^6 experiment) of ionized tetraethylsilane (m/z 144). Each spectrum shows the consecutive loss of an ethylene or ethyl group from the activated ion. The final stage of dissociation results in the formation of SiH^+ (m/z 29).

molecular ion was converted through a series of six stages of dissociation into the phenyl cation. On a different chemical system, MS^{12} has been demonstrated using a quadrupole ion trap![14]

Laser-induced ionization and photodissociation may conveniently be performed in ion traps using a fiber optic inserted through an aperture in the ring electrode.[15] Photoactivation allows more selective energy deposition than collisional activation, and the fact that the ions being irradiated are trapped makes it a much more efficient experiment than in the case where a fast moving beam of ions is photodissociated. In this respect, as in many others, a close analogy exists with ICR instruments where photoionization and photodissociation are well-developed techniques.[16]

Ion/Molecule Reactions

Ion traps are remarkably versatile devices in which many chemical processes besides collision-activated dissociation can be performed. Ion/molecule reactions are the most "chemical" part of mass spectrometry,[17] traditionally studied in high-pressure and chemical-ionization ion sources, as well as in flowing afterglow instruments, ICR spectrometers, and triple quadrupoles. The quadrupole ion trap offers access to both pressure- and time-dependent data on mass-selected ion populations, which enhances its potential as a device for the study of ion/molecule reactions. Not only can the reagent *ion* be selected but selected *neutral reagents* can also be delivered to the trap by using pulsed valves which have response times (fwhm) of less than 100 ms.[18]

Chemical ionization (CI), the ionization method based on ion/molecule reactions, is readily implemented in the ion trap.[19-21] With an appropriate sequence of rf

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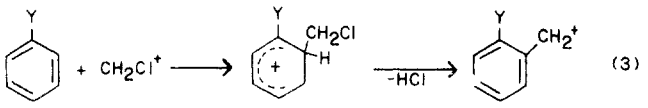
voltages and reaction times, the reagent ion is formed and mass-selected at relatively low reagent-gas pressures (typically 10^{-6}–10^{-4} Torr). These selected reagent ions then undergo ion/molecule reactions with the analyte during a second reaction period. Reagent ions can be chosen to cause proton transfer, charge exchange, and other desired reactions.

Ion/molecule reactions in the ion trap are of intrinsic interest as well as being of interest for comparison with chemical reactions in the condensed phase. A representative case is the halomethylation of various aromatic compounds with CH_2Cl^+ as the reagent ion. This reaction is followed by rapid dehydrohalogenation as shown in eq 3.[22] The influence of the aromatic substituent upon reaction was studied by using CAD to probe the structures of the product ions. As expected for electrophilic aromatic substitution, methyne addition is favored by electron-donating substituents.



(3)

The long times and relatively high operating pressures of the ion trap allow chemical equilibria to be established. For example, proton transfer between 2-ethylpyridine and 3-methylpyridine is complete after 500 ms in a typical experiment, and from this type of data relative gas-phase basicities can be determined.[22] Thermochemical data agree well with literature values; for example, the difference in proton affinity between 3-methyl- and 2-ethylpyridine was found to be 2.1 kcal mol^{-1} while the reported value is 2.2 kcal mol^{-1}.[23] An alternative method of determining thermochemical quantities, also readily implemented on the ion trap, utilizes the kinetics of dissociation of a cluster ion.[24] For example, relative proton affinities can be measured by generating a proton-bound dimer of the base of interest and a reference base, mass-selecting this cluster ion, and collisionally activating it to cause preferential dissociation into the protonated base with the greater basicity. As a time-based spectroscopic method, it is natural that progress has been reported in measuring the rates of ion/molecule reactions in the ion trap.[25] However, much remains to be learned about the capabilities of traps in this application.

Desorption Ionization

It is well-known that the development of the family of techniques known as desorption ionization (DI) has had a major influence in expanding the scope of mass spectrometry, particularly for biological compounds. For the ion trap to function as a general-purpose mass spectrometer, desorption ionization must be possible. Therefore, after development of MS/MS and chemical ionization capabilities, desorption ionization was implemented by generating ions in an external ion source and then injecting these ions into the ion trap.[26] External ionization has the advantage that the conditions for ionization can be optimized independently of those that must be maintained in the trap itself. Removal of kinetic energy from the ions once they enter the trap so they can adopt stable trajectories is facilitated by the fact that the trap is operated at 10^{-3}-Torr pressures especially when comparison is made with the analogous experiment in the Fourier transform ICR spectrometer.[27]

The most widely used and most successful desorption methods are fast atom bombardment (FAB) and liquid secondary ion mass spectrometry (SIMS), which utilize a fast atom or fast ion, respectively, to desorb analyte from solution. This experiment was first demonstrated with an ion trap using[28] Cs^+ projectiles, the pulsed cesium source being mounted externally to the ion trap. The desorbed sample and matrix ions are injected into the trap via a simple lens system. This method of ionization has proven to be very successful as will be evident from the examples given in later sections.

Mass Range Extension

In this Account of developments in quadrupole ion traps over the past six years, we have described how the simple GC detector was transformed into an MS/MS instrument capable of chemical and desorption ionization. These capabilities were added without loss of the inherent high sensitivity of the device, a consequence of the Felgett advantage arising from ion storage and minimal ion loss during mass analysis. In 1988 the principal remaining disadvantage of the device was its limited mass/charge range of 650 Da/charge (Da ≡ dalton). The highest mass analysis reported (m/z ca. 1200) had been achieved by Todd and co-workers[29] using a technique termed "reversed-scanning".

At the 1988 triennial Mass Spectrometry Conference, we undertook the objective to extend the mass/charge range of the ion trap to 10 000 within one year.[30] We relied on the joint efforts of our laboratory, that of George Stafford at Finnigan, and that of Phil Hemberger at Los Alamos and planned to use a combination of methods, each of which is evident by inspecting the mass analysis equation (1). It is possible to increase the mass range in four ways: (i) by increasing the maximum rf voltage, (ii) by decreasing the rf frequency, (iii) by adjusting the dimensions of the trap, viz., r_0, and (iv) by selecting a different point on the stability diagram to cross from stability to instability rather than the normal q_{eject} value of 0.91.

The first two methods for mass range extension require major changes in electronics and have not been

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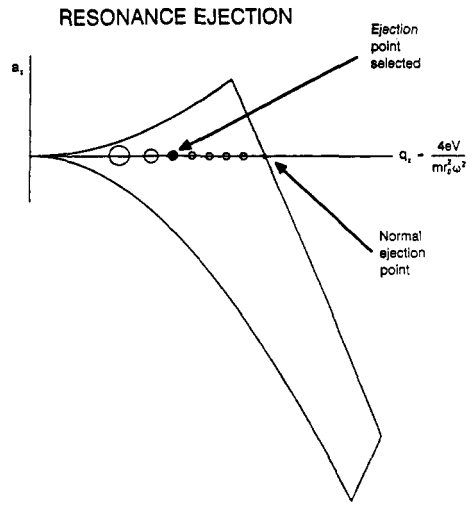

Figure 4. Resonance ejection causes ions to be unstable before they reach the stability boundary and so increases the mass/charge range.

studied in detail. A straightforward way to increase the mass range is to decrease the internal dimension of the ion trap (method iii). From eq 1, a 2-fold decrease in the internal radius (r_0) of the trap should yield a 4-fold increase in the mass-to-charge ratio. This method was studied in collaboration with the group at Los Alamos, where three sets of "small" electrodes were constructed with dimensions of one-half, one-third, and one-fourth that of the commercial electrodes. The smallest of these ion traps has an internal radius of just 2.5 mm![31] The expected increase in mass range was observed at rather small cost in resolution and sensitivity.

The fourth method for mass range extension, ejecting ions at lower q_{eject} values than normal, adapted a technique for improving resolution and sensitivity known as resonance ejection or "axial modulation".[32] We chose, however, to apply a supplementary ac voltage of low frequency causing resonant ejection of ions at q_{eject} values far below those that correspond to the normal stability limit (Figure 4). In this way, ions are ejected from the ion trap, not because they fall outside the confines of the stability diagram (as in the normal mass selective instability experiment), but rather, ions are resonantly excited and ejected when the secular frequency of the trapped ion is scanned through the applied frequency of the supplementary ac. Note that the supplementary ac voltage is applied across the end-cap electrodes in the same way as the supplementary ac voltage used to resonantly excite ions for MS/MS experiments. However, in the former experiment the supplementary voltage is applied during the rf scan and it utilizes much higher excitation amplitudes (typically 6–10 V_{p-p}). Mass limits in excess of 45 000 Da have been achieved by using resonant ejection[33] without changing the physical dimensions of the ion trap.

The increase in mass range available by these techniques allows one to utilize the full advantages of desorption ionization in the ion trap. Desorption of CsI clusters using 7-keV Cs^+ ions in a SIMS experiment

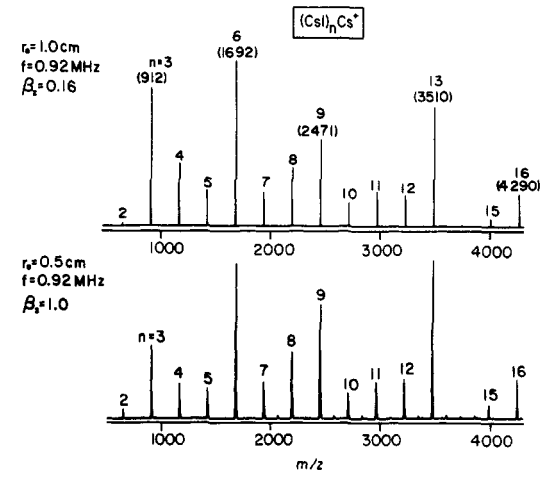

Figure 5. Comparison of Cs^+-desorbed CsI spectra obtained from two different methods of extending the mass range of the ion trap. The mass range in the top spectrum is increased by using resonance ejection, whereas the bottom spectrum shows mass range extension by halving the radius of the commercial electrodes. The conditions for trapping are identical in both experiments.

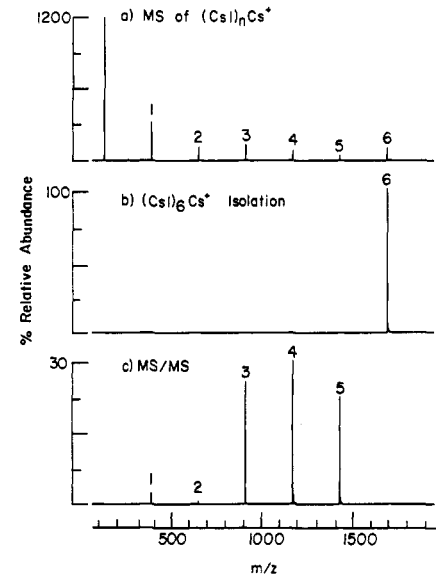

Figure 6. MS/MS daughter spectrum of $(CsI)_6Cs^+$ (m/z 1693) (50 ms, 3 V_{p-p} excitation).

demonstrates the analysis of high-mass ions. Figure 5 illustrates mass spectra of clusters of CsI to compare the two methods of extending the mass/charge mass range. Note that the frequency was reduced slightly from the standard 1.1 MHz to 0.92 MHz for both experiments, resulting in a further small increase (30%) in range. Note, in passing, the greatly enhanced abundances of certain clusters compared with others. For example, n = 13, which has 27 atoms and can adopt a 3 × 3 × 3 crystallite structure, is strongly favored.

MS/MS can be performed at high mass, exactly as it is done at low mass. An example of this is shown in Figure 6 where $(CsI)_6Cs^+$ (m/z 1693) is isolated and resonantly excited with an appropriate supplementary ac voltage. The excited ions undergo energetic collisions, and the resulting population of fragment ions is mass-analyzed by the usual mass selective instability scan except that axial modulation is used to increase the mass range. The degree of fragmentation can be selected by using the amplitude of the activating voltage or the activating period. Note the almost quantitative

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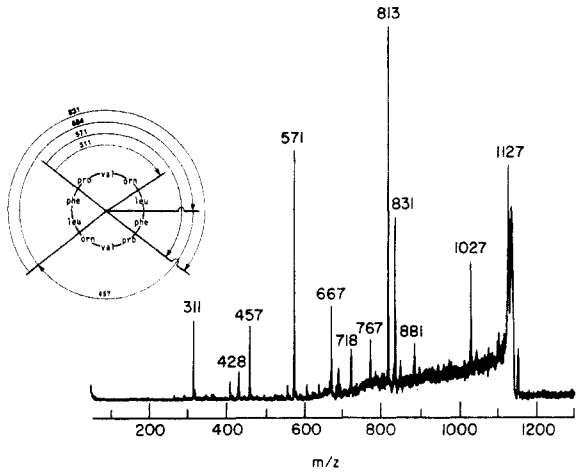

Figure 7. MS/MS spectrum of 2 fmol of gramicidin S acquired by using Cs^+ SIMS ionization. The insert illustrates the structure of this cyclic peptide and its major fragmentation pathways. Resonance ejection was used for mass range extension.

conversion of the 6-mer to fragment ions.

Analysis of Peptides

The characterization of peptides not only is a significant and rapidly growing area of application of mass spectrometry but also calls for the utilization of the three principal capabilities that have been added to mass spectrometers recently, viz., (i) MS/MS and MS^n capabilities, (ii) desorption methods of ionization, and (iii) an extended mass range. These capabilities have recently been added to the ion trap, which also offers (i) extreme sensitivity, (ii) demonstrated high-mass capabilities (in excess of m/z 45 000), (iii) collisional dissociation efficiencies in small molecules which approach 100%, (iv) availability of appropriate ionization techniques, i.e., Cs^+ SIMS and laser desorption, and (v) the ability to *accumulate* ions in the ion trap. This last feature should result in lower detection limits than seen with "beam-type" instruments, including the commonly used multiple sector or multiple quadrupole mass spectrometers. This attribute is particularly valuable for the analysis of biological materials where only small amounts of sample may be available.

Early results, such as that shown in Figure 7, encourage optimism regarding the trap's capabilities; here is shown the MS/MS spectrum of 2 fmol of gramicidin S, a cyclic peptide ionized by Cs^+ SIMS. The insert illustrates the structure of this peptide and the fragmentation of the $(M + H)^+$ parent ion to yield sequence-specific daughters. In a separate experiment, 250 amol (ca. 10^8 molecules) of this peptide gave reasonable MS/MS data; however, the number of structurally specific daughter ions was fewer.[33] Peptides up to m/z 4000 have been dissociated with high efficiency in the ion trap. This is illustrated by the data shown in Figure 8, where just 250 fmol of bovine insulin B-chain, a 30 amino acid peptide (MW = 3496), was loaded onto the sample probe. Note the occurrence of characteristic sequence ions, denoted in the usual way.[34] Multiple stages of collisional activation allow more complete sequence information to be obtained on a large peptide than when only a single activation step is used, and up to six stages of MS have been recorded for peptides.

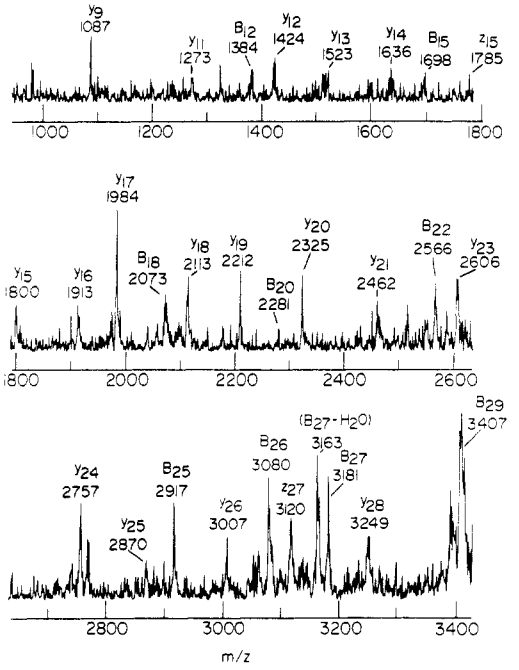

Figure 8. MS/MS spectrum of 250 fmol bovine insulin chain B (MW = 3496), ionized by Cs^+.

If one turns one's attention from the structural analysis of biomolecules to molecular weight determination above 5000 Da, Cs^+ SIMS may not be the ionization method of choice. One method of extending the molecular weight range is by increasing the number of charges carried by an ion. Electrospray techniques have been used to measure molecular weights for ions of m/z 900 which have up to 20 charges, so providing molecular weight information on compounds up to 18 000 Da using the ion trap.[35] Another alternative, which requires true extension of the mass/charge range, is matrix-assisted laser desorption. Nicotinic acid, which absorbs at a wavelength of 266 nm, the wavelength of the quadrupled YAG laser line, has been used to acquire molecular weight (but again not sequence) information on peptides above 200 kDa using time-of-flight mass spectrometry.[36] Initial experiments using matrix-assisted laser desorption with an ion trap have shown promising results, e.g., bovine insulin chain B shows a prominent protonated molecule when ionized from nicotinic acid matrix with a Nd:YAG laser at 266 nm.

Conclusions

The last six years have witnessed very rapid advances in ion-trap technology. Ion traps are proving valuable for analytical applications and for fundamental studies of gas-phase ion chemistry. The sensitivity, efficiency of collisional activation, high-mass capabilities, and availability of numerous ionization techniques are compelling reasons for the usefulness of the ion trap. The ability to perform MS^n scans allows great flexibility in tailoring experiments to address problems of increasing complexity. High-mass capabilities combined with efficient collisional activation offers a relatively

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inexpensive alternative to multiquadrupole and multisector instrumentation for the structural analysis of peptides and other biopolymers.

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The Unusual and the Unexpected in an Old Reaction. The Photochlorination of Alkanes with Molecular Chlorine in Solution[1]

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The photochlorination of an alkane, RH, with molecular chlorine in solution has long been recognized to be a radical chain reaction:[3]

initiation

$$Cl_2 \xrightarrow{h\nu} 2Cl^\bullet \quad (1)$$

propagation

$$Cl^\bullet + RH \rightarrow HCl + R^\bullet \quad (2)$$

$$R^\bullet + Cl_2 \rightarrow RCl + Cl^\bullet \quad (3)$$

termination

$$Cl^\bullet + Cl^\bullet \rightarrow Cl_2 \quad (4)$$

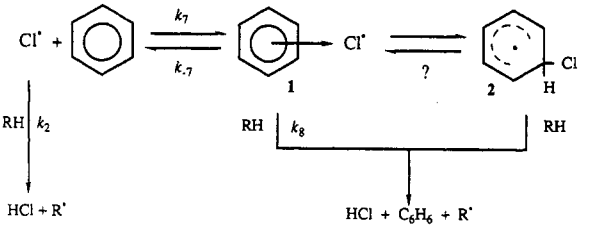
$$Cl^\bullet + R^\bullet \rightarrow RCl \quad (5)$$

$$R^\bullet + R^\bullet \rightarrow R_2 \quad (6)$$

After reviewing the earlier literature,[4] Haas, McBee, and Weber in 1936 provided more precise measurements of their own on some simple alkanes and formulated a series of important chlorination rules.[4,5] In somewhat abbreviated form, the four main rules for solution chlorinations are as follows:

1. Carbon skeleton rearrangements do not occur, but every possible monochloride is always formed.
2. Hydrogen atoms are always substituted at rates that are in the order primary < secondary < tertiary.
3. At increasing temperatures, these relative rates approach 1:1:1.
4. Moisture, carbon surfaces, and light have no effect upon these product ratios.

Scheme I



These rules are easy to understand. The first three imply that reactions 2 and 3 are fast and that the Cl• atom is a rather unselective hydrogen-abstracting agent while rule 4 is consistent with our expectations for a chain reaction that has a long chain length.

The Haas, McBee, and Weber chlorination rules remained unchallenged for over 20 years. Then, in 1957, Russell[6] showed that whereas product ratios might not depend on moisture, carbon surfaces, or light, they certainly did depend on the solvent used for the photochlorination. Specifically, Russell[6-8] showed that, in the photochlorination of 2,3-dimethylbutane (DMB), the tertiary/primary selectivity, S^m,[9] could be increased by working in aromatic solvents (and in CS_2). For example,[7] Russell found that at 25 °C S^m increased from 0.7 in pure liquid DMB to 10 for DMB in 8 M benzene. Russell proposed an equilibration between the "free" chlorine atom and a chlorine atom/arene π-complex,

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(3) In 1930, the photochlorination of $CHCl_3$ in CCl_4 was shown to have a very large quantum yield and a chain reaction involving Cl• and $Cl_3C^\bullet$ was proposed; see: Schwab, G. M.; Heyde, U. *Z. Phys. Chem., Abt. B* **1930**, *8*, 147–158.
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(9) S^m refers to the molecular tertiary/primary chloride product ratio, i.e., S^m = [2-chloro-DMB]/[1-chloro-DMB].

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